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ADULT UROLOGY

QUANTITATIVE ASSESSMENT OF UROFLOW: IS THERE A CIRCADIAN RHYTHM?

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ABSTRACT

Objectives. To investigate if the circadian rhythm of urinary flow values varies within groups of patients with varying degrees of bladder outlet obstruction.

Methods. A total of 170 patients with lower urinary tract symptoms suggestive of bladder outlet obstruction used a home-based uroflowmeter and produced a total of 1670 correctly measured flows at home. These patients also underwent a screening program with free urinary flowmetry in the hospital and a urodynamic pressure and flow study.

Results. There is a circadian variability in urinary flow values in men with higher grades of obstruction. These men have a higher peak urinary flow with a smaller voided volume and thus a shorter flow time in the early afternoon when compared with late evening, early morning, and the midnight to morning periods.

Conclusions. This significantly greater maximum flow in the afternoon in men with higher grades of obstruction can be an important bias in studies where the primary end point is to assess a small improvement in maximum flow. Therefore, the circadian rhythm of uroflow has to be taken into account in the evaluation of the efficacy of treatment. Patients participating in clinical research studies should produce their urinary flow in the clinic always during the same time period, either in the morning or in the afternoon, and should not switch their appointment time. UROLOGY **50**: 221–228, 1997. © 1997, Elsevier Science Inc. All rights reserved.

Single uroflowmetry may not be sufficiently reliable for the determination of bladder outlet obstruction (BOO) because many patients are unable to relax and void in the normal fashion while at the clinic. Therefore, Blaivas[1] has suggested that multiple samples are most efficient for enhancing an accurate assessment. For this reason, many units have developed urine-flow clinics to obtain multiple uroflowmetry results. Although this approach increases the number of reliable measurements, it is still not an ideal situation because it is both time-consuming for the patient and doctor and the patient is still not voiding under "normal conditions." To overcome these problems, several home-based systems of uroflowmetry have been introduced.[2–5] We recently reported on a system designed and developed to provide reliable results; it is easy to use by the patient at home, has quality-control of flow measurement, is handheld for practical use, uses hygienic disposable beakers, and gives results that are quickly and easily available.[4] However, it was concluded that, when multiple samples are available, the problem arises as to which sample(s) should be used for the evaluation, particularly if the reported circadian changes are of clinical relevance.[2,5–7]

In the present study, the results from the aforementioned portable home-based uroflowmeter were used to evaluate circadian changes in uroflowmetry parameters in patients with lower urinary tract symptoms. Furthermore, we investigated if circadian changes vary within various obstruction groups according to the Schäfer[8] linear passive urethral resistance relation (LPURR) nomogram.

PATIENTS AND METHODS

A total of 170 consecutive patients (mean age 62 years, range 38 to 80) with voiding complaints were seen in the outpatient department; all were evaluated initially by a medical history, an International Prostate Symptom Score (IPSS), a physical examination including digital rectal examination and transurethral ultrasonographic examination of the pros-

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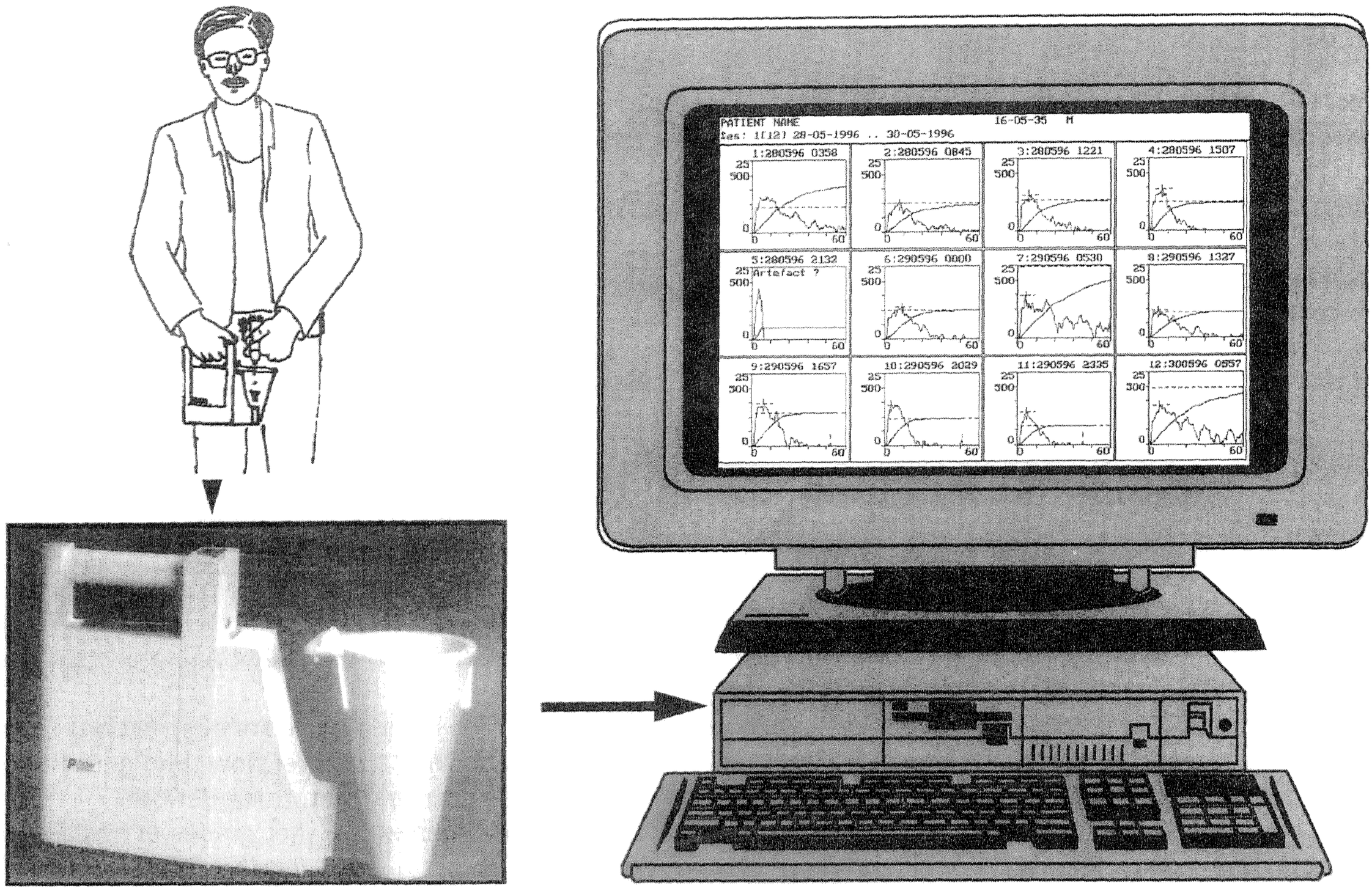

FIGURE 1. *Demonstration of the P-flow.*

tate, one free urinary flowmetry in the hospital, a urodynamic evaluation (including pressure-flow studies), and a series of measurements from the home-based uroflowmeter. Prostate volume was calculated using the planimetric method with a Kretz Combison 330 ultrasound scanner (Kretztechnik AG, Zipj, Austria) with a multiplane three-dimensional rectal transducer (VRW 177AK). For free urinary flowmetry in the hospital, the Dantec Urodyn 1000 flowmeter was used. Home-based uroflowmetry was performed with the home-based uroflowmeter, P-flow (Bioprocon, Wychen, The Netherlands).[4] Patients were supplied with the home-based uroflowmeter and 12 disposable beakers and were instructed to use the home-based flowmeter at 12 consecutive flows during 2 or 3 days. The patients were asked to start producing flows in the morning and to void "as they would normally do." The results of the uroflowmetry readings were stored in the home-based uroflowmeter and transferred to a computer for analysis during the second visit to the outpatient department (Fig. 1). When the patient used the home-based uroflow system incorrectly, an automatic artifact-detection program indicated whether an artifact could be expected. The home-based uroflowmeter has been described in detail previously.[4] Excluded were patients previously treated with transurethral (laser) resection of the prostate, transurethral microwave thermotherapy, or 5 alpha-reductase inhibitors. Patients using alpha$_1$-receptor antagonists were also excluded.

Urodynamic investigations were performed using an 8F transurethral lumen catheter and an 8F transrectal catheter both equipped with a microtip pressure sensor (MTC, Dräger, Best, The Netherlands). Before cystometry, the bladder was emptied through the lumen of a transurethral catheter to quantify residual urine after free uroflowmetry. The pressure sensors were zeroed to atmospheric pressure before introduction. The bladder was filled with water of 20°C with a filling speed of 50 mL/min with the patient in the supine position. Filling was stopped when the patient expressed a strong urge to void; micturition in the standing position was allowed in private. Digitally stored data were analyzed with equipment developed at our department. To get useful information from pressure-flow study curves, it was necessary to relate detrusor pressure to corresponding flow. To quantify the grade of outlet obstruction, we used the concept of the LPURR, relating minimal urethral opening pressure observed at the end of voiding with detrusor pressure at maximum flow.[8] Patients in LPURR classes 0 and 1 had no BOO, patients in classes 2 and 3 had moderate BOO, and patients in higher classes had severe obstruction. We also used the urethral resistance factor (URA) for grading bladder outlet obstruction. Calculation of URA was based on the point of maximum flow and corresponding detrusor pressure.[9] A URA value greater than 29 cm H_2O indicated obstruction.

Circadian changes were examined by dividing the 24-hour recording period into four periods, with daytime periods 1 to 4 corresponding to midnight to 6 AM (night), 6 AM to noon (morning), noon to 6 PM (afternoon), and 6 PM to midnight (evening). The following parameters were evaluated for each of the obstruction categories: voided volume, maximum flow, mean flow, and flow time. Mean values of these parameters were calculated for each daytime period per patient. These mean values were used to calculate the mean of the studied population. Descriptive statistics were used to illustrate the studied population. The Kruskal-Wallis one-way analysis of variance test, the Wilcoxon matched-pairs signed-rank test, and the Wilcoxon rank-sum W test were used for the statistical analysis.

RESULTS

A total of 170 patients with a median prostate volume of 34 mL (range 16 to 120) and a median

TABLE I. *The median number (range) of flows per patient for each daytime period as well as the total number of flows within each obstruction category*

Category	Midnight–6 AM	6 AM–Noon	Noon–6 PM	6 PM–Midnight	Total
LPURR = 0, 1	1.0 (0–4)	2.0 (0–5)	3.0 (0–6)	3.0 (0–6)	10.0 (3–12)
(n = 64)	89	154	181	181	605
LPURR = 2, 3	1.0 (0–5)	3.0 (0–5)	3.0 (0–6)	3.0 (0–5)	11.0 (3–12)
(n = 70)	98	206	208	194	706
LPURR = 4, 5, 6	1.0 (0–4)	3.0 (1–6)	3.0 (0–6)	3.0 (0–6)	10.5 (4–12)
(n = 36)	49	108	105	97	359

KEY: LPURR = linear passive urethral resistance relation.

TABLE II. *Mean flow values for the flow produced in the hospital and for those produced at home for each daytime period indicated for each obstruction category**

	Hospital Flow	Midnight –6 AM	Wilcoxon *P* Value	6 AM–Noon	Wilcoxon *P* Value	Noon–6 PM	Wilcoxon *P* Value	6 PM–Midnight
Voided volume (mL)	***P* <0.01**	***P* = 0.14**		***P* <0.01**		***P* <0.01**		***P* <0.01**
LPURR = 0, 1	293	300	→ 0.25 ←	249	→ <0.01 ←	204	→ 0.12 ←	222
LPURR = 2, 3	240	277	→ <0.01 ←	209	→ <0.01 ←	189	→ 0.20 ←	198
LPURR = 4, 5, 6	191	232	→ <0.01 ←	167	→ 0.05 ←	143	→ 0.42 ←	149
Maximum flow (mL/s)	***P* <0.01**	***P* <0.01**		***P* <0.01**		***P* <0.01**		***P* <0.01**
LPURR = 0, 1	13.9	14.8	→ 0.57 ←	14.3	→ 0.13 ←	14.3	→ 0.96 ←	14.4
LPURR = 2, 3	11.1	11.9	→ 0.49 ←	11.9	→ <0.01 ←	13.0	→ 0.54 ←	12.7
LPURR = 4, 5, 6	7.9	7.6	→ 0.06 ←	8.3	→ 0.03 ←	9.6	→ 0.03 ←	8.7
Mean flow (mL/s)	***P* <0.01**	***P* <0.01**		***P* <0.01**		***P* <0.01**		***P* <0.01**
LPURR = 0, 1	7.2	8.4	→ 0.93 ←	7.8	→ 0.13 ←	8.0	→ 0.38 ←	8.2
LPURR = 2, 3	5.7	6.2	→ 0.23 ←	6.5	→ 0.03 ←	7.0	→ 0.72 ←	7.0
LPURR = 4, 5, 6	4.0	4.3	→ 0.03 ←	4.8	→ 0.02 ←	5.7	→ 0.05 ←	5.0
Flow time (s)	***P* = 0.09**	***P* <0.01**		***P* = 0.14**		***P* = 0.84**		***P* = 0.29**
LPURR = 0, 1	45	43	→ 0.15 ←	33	→ <0.01 ←	28	→ <0.01 ←	31
LPURR = 2, 3	46	49	→ <0.01 ←	37	→ <0.01 ←	30	→ 0.04 ←	32
LPURR = 4, 5, 6	55	63	→ <0.01 ←	40	→ <0.01 ←	29	→ 0.08 ←	33

KEY: LPURR = linear passive urethral resistance relation.

* *Bold P values indicate the comparison between obstruction groups (Krushal-Wallis one-way ANOVA test). Wilcoxon P values indicate the comparison between specific periods of time to the left and right of the P value (arrows) (Wilcoxon matched-pairs signed-rank test).*

IPSS score of 15 (range 1 to 33) received 12 beakers each and completed several micturitions free of artifacts. During a 2- or 3-day period, 3 to 12 (median 10) measurements were obtained from each patient. A total of 1850 flow measurements were recorded at home, and the quality-control system indicated that there were possible artifacts in 223 flows (12%). After visual evaluation of all flows by one of the authors (W.W.), there appeared to be 1670 (90%) correctly measured flows in total. The median number of registered flows per patient for each daytime period, as well as the total number of flows within each obstruction category, is indicated in Table I. This table shows that the number of flows produced at specific daytime periods was not significantly different between obstruction groups.

Table II and Figure 2 indicate the mean flow values for the flow produced in the hospital and the flows produced at home for each daytime period within obstruction categories. Except for voided volumes produced between midnight and 6 AM, the differences in voided volume and maximum flow between obstruction groups were all statistically significant (Table II). Severely obstructed patients (LPURR of 4 or more) had a significantly smaller mean voided volume and mean maximum flow.

Table II and Figure 2A show that, in all obstruction categories, the mean voided volume produced between midnight and 6 AM was significantly greater compared with the flows produced in the afternoon and evening, whereas the smallest mean voided volume at home is produced in the afternoon (Fig. 2A). For the groups without obstruction (LPURR of 0 or 1) and with moderate obstruction (LPURR of 2 or 3), mean voided volume produced at the hospital was significantly greater

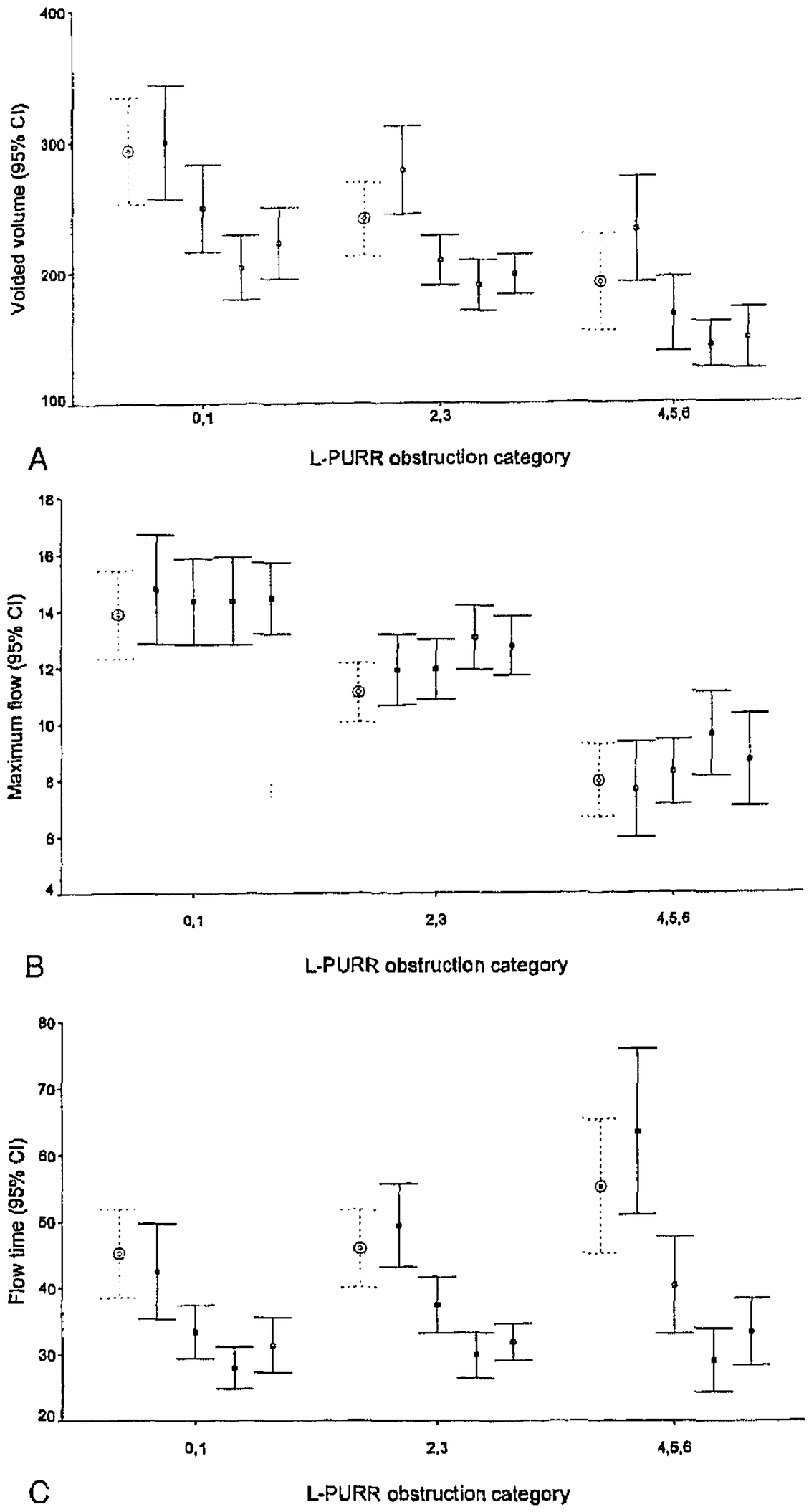

FIGURE 2. *(A) Mean voided volume, (B) maximum flow, and (C) flow time values and their 95% confidence intervals (CI) for each linear passive urethral resistance relation (L-PURR) obstruction category. The circle and dotted CI indicate the mean values for the flow produced at the hospital. The squares and the solid CIs indicate from the left to the right side, respectively, the mean values of the flows produced at night (from midnight to 6 AM), in the morning (6 AM to noon), in the afternoon (noon to 6 PM), and in the evening (6 PM to midnight).*

compared with that produced at home in the afternoon (Fig. 2A).

The mean maximum flow in patients without obstruction was not significantly different between specific daytime periods (Table II, Fig. 2B). In the patients with moderate and severe obstruction, the maximum flow produced at home in the afternoon was significantly greater than that produced in the morning. Moreover, in severely obstructed patients, the maximum flow in the evening was again significantly smaller (Fig. 2B).

In the moderately and severely obstructed patients, the significantly greater mean voided volumes and smaller mean maximum flow values between midnight and 6 AM resulted in statistically significant differences in mean flow time in that period but not in other periods of the day. Severely obstructed patients had approximately a doubling of their flow time between midnight and 6 AM when compared with the afternoon and evening. This difference was less pronounced in patients who were not obstructed. Mean flow time at the hospital was comparable with that produced at home between midnight and 6 AM (Fig. 2C).

We further investigated the group with extreme differences in voided volume and maximum flow between the flows produced in the morning and those produced in the afternoon. The median absolute difference for voided volume was 50 mL and for maximum flow 2 mL/s. As indicated by statistically significant differences in the urodynamic values for detrusor pressure at maximum flow, URA, and LPURR obstruction category, the group with absolute differences in voided volume exceeding 50 mL and in maximum peak exceeding 2 mL/s was significantly less obstructed compared with those without extreme differences, whereas the other clinical parameters of age, total IPSS, and prostate volume were not significantly different (Table III).

We also investigated differences between patients who had a voided volume of over 150 mL in less than 50% of the flows produced at home versus those with voided volumes over 150 mL in 50% or more of the flows produced at home. A total of 125 patients (74%) had voided volumes over 150 mL in 50% or more of the flows produced at home. Patients who had voided volumes over 150 mL in less than 50% of the flows had significant differences in the urodynamic values of bladder capacity, detrusor pressure at maximum flow, URA, and LPURR obstruction category, indicating that they were more obstructed compared with those who had voided volumes over 150 mL in 50% or more of the flows. The other clinical parameters of age and prostate volume were not significantly different among both groups (Table IV). Total IPSS was significantly greater in those who had voided volumes over 150 mL in less than 50% of the flows. When evaluating the specific symptoms, it appeared that this significant greater total symptom score originated mainly from symptoms related to frequency: repeated urination, urge, and nocturia. All these symptoms were significantly more frequently reported than in those who had voided volumes over 150 mL in 50% or more of the flows.

TABLE III. *Patient characteristics of the groups of patients with and without extreme absolute differences in voided volume and maximum flow*

	Difference in Morning/Afternoon Voided Volume ≤50 mL (n = 73)	Difference in Morning/Afternoon Voided Volume >50 mL (n = 86)	Difference in Morning/Afternoon Maximum Flow ≤2 mL/s (n = 81)	Difference in Morning/Afternoon Maximum Flow >2 mL/s (n = 76)
Age (yr)	62 ± 8	61 ± 9	63 ± 9	60 ± 8
Total IPSS score	15.9 ± 6.7	15.7 ± 6.5	15.5 ± 6.4	16.1 ± 6.8
Prostate volume (mL)	41 ± 17	40 ± 22	43 ± 22	39 ± 18
Bladder capacity (mL)	365 ± 117	419 ± 132*	383 ± 110	407 ± 145
Detrusor pressure at maximum flow (cm H_2O)	58.2 ± 30.5	45.8 ± 20.0*	55.0 ± 25.3	47.0 ± 25.8*
URA (cm H_2O)	37.4 ± 20.9	29.9 ± 16.1*	36.3 ± 19.5	29.4 ± 16.0*
LPURR category	2.5 ± 1.6	1.9 ± 1.3*	2.4 ± 1.5	1.9 ± 1.4*

KEY: IPSS = International Prostate Symptom Score; LPURR = linear passive urethral resistance relation; URA = urethral resistance factor.
** Indicates significant difference (P <0.05) between groups (Wilcoxon rank-sum W test).*

TABLE IV. *Patient characteristics of the groups of patients with less than 50% of the voided volumes produced at home over 150 mL (n = 45) and those with 50% or more of the voided volumes produced at home over 150 mL (n = 125)*

	<50% of the Voided Volumes Produced at Home >150 mL	≥50% of the Voided Volumes Produced at Home >150 mL
Age (yr)	61 ± 9	62 ± 8
Total IPSS score	19.0 ± 7.7	14.6 ± 5.9*
IPSS 1; incomplete emptying	2.4 ± 1.8	1.8 ± 1.6
IPSS 2; repeated urination	3.4 ± 1.5	2.5 ± 1.5*
IPSS 3; intermittency	2.7 ± 2.0	2.2 ± 1.6
IPSS 4; urge	3.1 ± 2.0	1.9 ± 1.7*
IPSS 5; reduced stream	3.7 ± 1.6	3.2 ± 1.5
IPSS 6; strain to start	1.5 ± 1.6	1.2 ± 1.3
IPSS 7; nocturia	2.4 ± 1.3	1.9 ± 1.1*
Prostate volume (mL)	44 ± 25	39 ± 17
Bladder capacity (mL)	307 ± 91	428 ± 123*
Detrusor pressure at maximum flow (cm H_2O)	63.9 ± 34.9	46.3 ± 19.5*
URA (cm H_2O)	43.1 ± 26.3	29.1 ± 13.2*
LPURR category	2.8 ± 1.9	1.9 ± 1.3*

KEY: IPSS = International Prostate Symptom Score; LPURR = linear passive urethral resistance relation; URA = urethral resistance factor.
** Indicates significant difference (P <0.05) between groups (Wilcoxon rank-sum W test).*

The effect of excluding flows with voided volumes of less than 100 mL and of less than 150 mL on the mean voided volume and maximum flow produced in the morning and afternoon is indicated in Table V.

COMMENT

For decades, uroflowmetry has played a major role in the evaluation of patients with lower urinary tract symptoms. Urologists use uroflowmetry measurements, together with patient symptoms and other clinical findings, to decide on the need for therapeutic intervention. Most urologists nowadays agree that only patients with BOO should undergo surgical intervention[10]; nevertheless, the decision for surgery is usually based primarily on the nature and severity of symptoms and the results of uroflowmetry. A urodynamic investigation with pressure-flow study analysis is considered to be the reference standard to determine BOO.[11]

TABLE V. *The effect of excluding flows with voided volumes of less than 100 mL and of less than 150 mL on mean flow values ± standard deviation for the flows produced in the morning and the afternoon in the obstruction categories**

	All Flows (1670 flows)			Flows <100 mL Excluded (1477 flows)			Flows <150 mL Excluded (1087 flows)		
	Morning	*P* Value	Afternoon	Morning	*P* Value	Afternoon	Morning	*P* Value	Afternoon
Voided volume (mL)									
LPURR = 0, 1	249 ± 128	<0.01	204 ± 96	275 ± 120	<0.01	225 ± 91	316 ± 114	<0.01	258 ± 84
LPURR = 2, 3	209 ± 79	<0.01	189 ± 80	228 ± 83	<0.01	203 ± 78	261 ± 73	<0.01	229 ± 71
LPURR = 4, 5, 6	167 ± 84	0.05	143 ± 50	198 ± 72	<0.01	158 ± 43	229 ± 66	<0.01	191 ± 28
All patients	214 ± 105	<0.01	185 ± 84	239 ± 100	<0.01	202 ± 81	275 ± 95	<0.01	234 ± 75
Maximum flow (mL/s)									
LPURR = 0, 1	14.3 ± 5.9	0.13	14.3 ± 6.0	15.4 ± 5.3	0.33	15.2 ± 5.7	16.2 ± 5.4	0.12	16.5 ± 5.5
LPURR = 2, 3	11.9 ± 4.4	<0.01	13.0 ± 4.6	12.2 ± 4.5	<0.01	13.6 ± 4.4	12.4 ± 4.5	<0.01	14.5 ± 4.9
LPURR = 4, 5, 6	8.3 ± 3.4	0.03	9.6 ± 4.3	8.4 ± 3.0	0.12	10.0 ± 4.2	8.4 ± 3.1	0.01	11.3 ± 4.1
All patients	12.0 ± 5.3	<0.01	12.8 ± 5.4	12.6 ± 5.2	<0.01	13.4 ± 5.2	13.0 ± 5.4	<0.01	14.7 ± 5.3

KEY: LPURR = linear passive urethral resistance relation.
** P values indicate the comparison between the flows produced in the morning and afternoon (Wilcoxon matched-pairs signed-rank test).*

However, rather than performing this invasive investigation, uroflowmetry is most often used to document voiding disorders because it is simple to perform, the results are quickly available, and refined flowmeters are easy to use.[12] Besides its diagnostic role, uroflowmetry has evolved as one of the most important evaluation methods in the assessment of the efficacy of drug treatments and other therapies in patients with lower urinary tract symptoms. The most modern flowmeters allow the measurement of voided volume, maximum flow, mean flow, and flow time. Moreover, the flow pattern can be described. Among the many parameters, maximum flow is regarded as the most useful in assessing the degree of obstruction and in monitoring treatment effects. Despite its popularity, uroflowmetry is hampered by several difficulties, including its inability to differentiate between BOO and impaired detrusor activity, artifacts, reproducibility, and circadian changes.[2,5–7,13–16]

Golomb *et al.*[2] studied circadian changes in a group of patients with benign prostatic hyperplasia (BPH) and a group of healthy men. They reported in patients with BPH an increase in voided volume, interval to maximum flow, and flow time from midnight to 6 AM and a decrease in volume-adjusted peak flow from midnight to noon and in peak flow from 6 AM to noon. Nakamura *et al.*[5] reported typical circadian rhythms for most patients investigated. Most patients showed a decreased frequency at night and an increased voided volume in the early morning, which was considered the typical rhythm of urination. These investigators also showed that, from midnight to 6 AM, the frequency in elderly men was significantly greater than that in a middle-aged group. This increased frequency was primarily due to an increase in diuresis in the elderly men investigated.[6] Burgio *et al.*[7] reported a frequency of diurnal urination of 5.5 for the age category reported in the present study. Unfortunately, we were not able to report circadian changes in frequency or diuresis. In the present study, the total number of flow measurements obtained from each patient during a 2- to 3-day period was between 3 and 12 (median 10). This is less than what could be expected when the home-based uroflowmeter was used continuously for this period. Although the flowmeter was not used continuously by all patients and we cannot, therefore, report on circadian changes in frequency, some important findings can be gleaned from the present study.

We reported an increase in voided volume and flow time, both interrelated parameters, from midnight to 6 AM, which is in agreement with the results of Golomb *et al.*[2] and Nakamura *et al.*[5,6] Despite a clearly greater voided volume at night, maximum flow was not significantly greater.

There was a close relationship between voided volume produced between midnight and 6 AM and voided volume produced at the hospital. The greater voided volume produced at the hospital could be explained probably because the results were obtained under "forced" conditions. This is not surprising because the sole aim at the outpatient department in the hospital is to have the bladder as full as possible, whereas at home, the timing of micturition is related to other normal daily activities. The value of the "supranormal" values obtained under the conditions of the outpatient department may be questioned when they are used as inclusion criteria in treatment protocols.

In the present study, it was shown that there is a circadian variability in urinary flow values in men with higher grades of obstruction. These men have a higher peak urinary flow with a smaller voided volume and thus a shorter flow time in the early afternoon when compared with late evening, early morning, and the midnight to morning periods. This significantly greater maximum flow in the afternoon in men with higher grades of obstruction can be an important bias in studies where the primary end point is to assess a small improvement of maximum flow. Therefore, the circadian rhythm of uroflow has to be taken into account in the evaluation of the efficacy of treatment.

Circadian changes in voided volume and maximum flow result in marked differences in flow time. Whereas the differences between obstruction categories in flow time for the voidings produced at the hospital were not statistically significant, the difference in flow time for the voidings produced at home between midnight and 6 AM was statistically significant. Between midnight and 6 AM, severely obstructed patients have approximately a doubling of flow time compared with the flows produced in the afternoon and evening.

How can we explain this circadian variability? Kaplan and Kaplan,[17] based on the similarity of patterns of occurrence between hypertension and BPH, suggested a shared underlying mechanism. They stated that "There is substantial evidence that the sympathetic nervous system plays an important etiologic role in both hypertension and BPH. The level of sympathetic drive may have a circadian rhythm reaching a peak in the early morning, the time of the day at which most cardiovascular events occur." If this level of sympathetic drive really influences the lower urinary tract, the maximum flow of flows produced during the morning would be lower; this appeared to be true in our study. This circadian rhythm also exists in asthmatic patients, who experience a circadian variation with increased airway responsiveness and decreased lung function at night and the early morning compared with the rest of the day.[18] Future studies are needed to elucidate the pathophysiology of the circadian variation in patients with hypertension, asthma, and BPH.

Patients with extreme differences between the morning and afternoon flow were more likely to be without BOO. Obviously, patients without obstruction have greater voided volumes and greater maximum flows; consequently, a greater variability may be expected.

In the group of patients with severe obstruction, the flow produced in the afternoon had a mean voided volume of 143 mL with a standard deviation of 50 mL. This indicates that a considerable percentage of patients has an initial voided volume of less than 150 mL, a cutoff point that is frequently used as selection criterion in clinical trials. Evidently, some patients with obvious BOO do not enter these trials, whereas the largest urodynamic treatment responses are reported in patients with low maximal flow rates.[19] When the flows with voided volumes less than 150 mL are excluded from the analysis and the morning and afternoon results of flow at home are compared, it is clear that the improvement in maximum flow seems to increase. This may be explained by the fact that the afternoon flow has a significantly lower voided volume and relatively more flows are excluded in the afternoon because the volume is less than 150 mL, which may overemphasize the increase in maximum flow in the afternoon.

In the present study, patients who had voided volumes less than 150 mL in the majority of their flows were more obstructed than those who had voided volumes over 150 mL in the majority of their flows. Moreover, the total IPSS score was significantly smaller in the latter group. This smaller total IPSS score in patients who had voided volumes over 150 mL in the majority of their flows was primarily due to symptoms that are related to frequency: repeated urination, urge, and nocturia. All these symptoms were significantly less frequently reported in patients who had voided volumes over 150 mL in the majority of their flows. Obviously, there is a direct relationship between obstruction, lower voided volumes, and frequency. These results are in agreement with the results of El Din *et al.*,[20] who investigated the correlation between the diagnosis of BOO and individual symptoms of the IPSS. They concluded that there was a statistically significant correlation between the specific questions of the IPSS and objective grade of obstruction; in addition, the questions related to frequency (repeated urination, urge, and nocturia) showed better correlations with obstruction than did other questions. However, the clinical significance of this finding was considered to be doubtful because none of the Spearman rank-correlation coefficients was above 0.23, indicating

very weak correlations. Furthermore, there was considerable overlap of symptom scores between patients with different grades of BOO.[20] We agree with their conclusion that subjective and objective methods measure different aspects of the clinical condition that should be viewed separately in the evaluation and treatment decision for the symptomatic patient.

CONCLUSIONS

There is an important circadian variability in urinary flow values in men with higher grades of obstruction. These men have a higher peak urinary flow with a smaller voided volume and thus a shorter flow time in the early afternoon when compared with late evening, early morning, and the midnight to morning periods. This significantly greater maximum flow in the afternoon in men with higher grades of obstruction can be an important bias in studies where the primary end point is to assess a small improvement of maximum flow. Therefore, the circadian rhythm of uroflow has to be taken into account in the evaluation of the efficacy of treatment. Patients participating in clinical research studies should produce their urinary flow in the clinic always at the same time, either in the morning or in the afternoon, and should not switch their appointment time.

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